Atty. Docket No.: 3124-Z

AE IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Richard J. Feldmann

Serial No. 09/866,925 Group Art Unit 1645

Filed: May 30, 2001 Examiner John S. Brusca

For: Algorithmic determination of flanking DNA sequences that control the expression of sets of genes in prokaryotic, archea and eukaryotic genomes

AMENDED APPEAL BRIEF TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Attached hereto are three (3) copies of the AMENDED BRIEF ON APPEAL for the above-identified application. The fee in payment of the brief fee was paid earlier.

Any fees necessary to effect the proper and timely filing of this Brief may be charged to Deposit Account No. 26-0090.

Respectfully submitted,

Jim Zegeer

Jim Zegeer, Reg. No. 18,957
Attorney for Appellant

Attachments: Amended Brief on Appeal (3 copies)

Suite 108
801 North Pitt Street
Alexandria, VA 22314
Telephone: 703-684-8333

Date: August 5, 2005

In the event this paper is deemed not timely filed, the applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to Deposit Account No. 26-0090 along with any other additional fees which may be required with respect to this paper.

Atty. Docket No.: 3124-Z

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Richard J. Feldmann
Serial No. 09/866,925 Group Art Unit 1645
Filed: May 30, 2001 Examiner John S. Brusca
For: Algorithmic determination of flanking DNA sequences that control the expression of sets of genes in prokaryotic, archea and eukaryotic genomes

AMENDED
BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the final rejection mailed September 23, 2004 of Claims 20 - 37 of the above-identified application.

(i). The Real Party in Interest

The real party in interest is Global Determinants, Inc.

(ii). Related Appeals and Interferences

There are no related appeals or interferences.

(iii). Status of the Claims

Claims 20 - 37 are pending in the application and have been finally rejected and are all on appeal. Claims 1 - 19 have been cancelled.

(iv). Status of the Amendments

There was no amendment filed subsequent to the final rejection.

(v). Summary of Claimed Subject Matter

The invention is directed to a computer mediated method of identifying DNA sequences that control the expression of different collections of genes in a genome. DNA sequences of an organism (the genome thereof) are analyzed by computer to identify DNA control sequences, called C1, C2 in the algorithm which meets certain specific criteria set forth at pages 26-36 of the description. Further, identified sequences behave in such a way that when the control sequence (C1 and C2) is transcribed into RNA, the RNA will seek out and bind the target sequences T1 and T2 (C1 binding to T1 and C2 binding to T2) to achieve the effect that the entire DNA sequence beginning with T1 and ending with T2 is shielded from transcription.

(vi). Grounds of Rejection to be Reviewed on Appeal

The final rejection of claims 20 - 37 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention?

(vii). Argument

The claims stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, the Examiner citing *In re Wands, 8 USPQ2d 1400 (CAFC 1988)*.

The claims are all directed to computer mediated methods of genome investigation in which the tetradic relationship between two specific adjacent RNA single-stranded sequences interact with two different double-stranded DNA sequences. Claim 20 refers to a computer algorithm for identifying DNA sequences that control the expression of different collections of genes of a genome comprising detecting by computer one or more pairs of non-adjacent DNA sequences in which are bound one RNA molecule comprising two RNA sequences. *In re Wands* does <u>not</u> deal with computer mediated matters.

In rebuttal to the 35 U.S.C. §112, first paragraph, rejections, appellant submitted two declarations, one of Dr. Richard W. Pastor, and the second of James B. Oberthaler.

Both declarations traverse the Examiner's conclusion that undue experimentation is necessary in order to practice the invention. The Oberthaler[1] declaration concludes:

---

[1] Mr. Oberthaler has a minority interest (less than 10%) in a licensee of the invention.

Finally, in conclusion, I disagree with the Examiner's contention that the trial and error experimentation required to practice the invention amounts to undue experimentation for the following reasons:

(1) As stated earlier, the algorithms presented are straightforward and complete.

(2) No experimentation whatsoever is required. Implementing the algorithms is a routine exercise in program design, coding and debugging. Running them is simply a matter of obtaining the organism-specific genomes and allowing the computer programs to go to work on them.

(3) The only part of the activity that could conceivably be referred to as "experimenting" is the investigation into available bioinformatics resources, such as the syntax and semantics of the resources provided by, for example, that National Library of Medicine's National Center for Biotechnology Information (NCBI). It is clear that in this context, having a ready understanding of this information is a reasonable characteristic of one who could be called "skilled in the art."

(Note: Even *In re Wands* recognized that some experimentation is permissible. 84 USPQ 1400, at p. 1404.)

Dr. Pastor states as follows:

The skilled practitioner would turn to the instant description and drawings for guidance in using the claimed invention. The specification provides a detailed roadmap for practicing the invention by one skilled in the art. Referring specifically to the specification and drawings, the introduction at pages 1 - 3 provides a basic description of connectron structure. Figures 1 - 3 are taken from the text by Alberts et al. entitled "The Molecular Biology of the Cell." Pages 3 - 25. Pages 26 - 36 provides a detailed description of a connectron structure. Page 31, the detailed description of the invention, provides a descriptive analysis of the flow diagrams utilized in the computer analysis of connectrons in any given genome. Additionally, ten samples of connectrons found by computer mediation are set out in the specification. Pages 39 - 56 give an example of a prokaryote connectron - E. coli. hence, the algorithm is clearly defined and could be programmed by a skilled

> scientist. In this sense, the amount of experimentation is quite predictable.
>
> I agree that the nature of the invention, gene control, is complex, and that prior art does not discuss connectron symmetries; i.e., it is my understanding and belief that the connectron invention disclosed in the instant application was made by the inventor, Richard J. Feldmann. [The page references are to the original specification.]

To the extent that *In re Wands* applies to claims dealing with computer mediated genome matters, the Oberthaler and Pastor declarations rebut the Examiner's contention that undue experimentation is necessary in order to practice the invention. Both declarations clearly establish that a detailed roadmap for practicing the invention by one skilled in the art is given in the specification. Both declarations traverse the Examiner's conclusion that undue experimentation is necessary in order to practice computer mediating steps recited in the claims. The Oberthaler declaration establishes that one skilled in the art (a journeyman, molecular biologist, bioinformatician, or computer programmer who understands the storage format, content and use of readily available bioinformatics resources) can write software following the algorithm that will analyze the DNA sequence of an organism to identify DNA sequences (called C1, C2, T1, T2 in the description of the algorithm) meeting specific criteria set forth in the description. And, further, that the identified sequences behave in such a way that when the control sequence containing C1 and C2 is transcribed into RNA, the RNA will seek out and bind to

the target sequence (C1 binding to T1 and T1 and C2 binding to T2 to achieve the effect that the entire DNA sequence beginning with T1 and ending with T2 is shielded from transcription. (See page 4 of the Oberthaler declaration.)

In support of his contention, the Examiner refers to page 29, paragraph 113 of appellant's specification that: "The physical existence and lifetimes of the connectrons must be proved by molecular biological experimentation." This, however, is taken out of context. The full paragraph reads as follows:

> The physical existence and lifetimes of the connectrons must be proved by molecular biological experimentation. This physical experimentation process, however, is logically quite separate from the computational experimentation that have been conducted from June of 1999 to May of 2001. The computational search for the existence of connectrons has been extremely positive. These computations have shown that connectrons exist in prokaryotes, in archea, between prokaryotes and their plasmids, in single-celled eukaryotes, in multi-celled eukaryotes, in plants, in higher animals and in humans. All of these features and properties are described in the claims section that follows.

The physical experimentation process is quite separate from the computational experimentation that has been conducted. Appellant respectfully submits that these declarations fully refute the Examiner's contention that claims 20 - 37 contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected to make or use the invention and that undue experimentation is required.

With respect to the Examiner's contention that the description does not provide working examples of using identified connectron symmetry to predict effects on gene expression (page 3 of Office action), item subparagraph c)), Mr. Oberthaler states:

> I disagree. On the contrary, this is exactly what the examples provide. As explained in the introduction and in the definitions provided, (particularly, the definitions of Possible Connectron and Hierarchy of Connectron Action) each connectron control sequence C1-C2 will, when transcribed into RNA, seek out and bind to its target sequence T1-T2, thereby shielding the DNA between T1 and T2 from transcription. Since the shielded DNA sequence will not be transcribed, any genes in the span between T1 and T2 will not be expressed as proteins for as long as the C1-C2 sequence remains bound to T1-T2. Similarly, any additional C1-C2 sequences in the span between T1 and T2 will also remain inactive during this time period, and therefore the inability effect they otherwise would have exerted on their target sequences will be suppressed during this time period. Granted that the full, cascading sequence of transcription/expression and sequestration that would result from each of the examples discussed is not presented, the principles are given that would enable anyone who understands the mechanism, as explained in the application, to follow the effects as deeply as he or she desires.

Claim 21 is directed to a computer mediated method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising, by computer, detecting changes in connectron behavior in a genome as a function of changes in the sequence of the genome.

Claim 22 differs in that this claim is directed to a computer mediated method of detecting changes caused by the application of an exogenous stimulus.

Claim 23 differs in that this claim is directed to a method of detecting by computer where and when new genes have been integrated into a host genome comprising detecting an operable link between a newly introduced gene and a preexisting connectron behavior in the host genome.

Claim 24 is directed to a computer mediated method of detecting the expression effect of different gene collections comprising detecting by computer the effect of connectrons on transcription.

Claim 25 is directed to a method of changing the expression of different gene collections in a genome by identification of connectron organization.

Claim 26 is directed to a method of detecting connectron control and target sequences in a given genome by computer, determining the base composition of the genome, determining one or more sites of control sequence organization, and/or determining one or more sites of target application.

Claim 27 is directed to a computer mediated method of determining the response of a cell in any tissue to changes in the cell's environment and/or genetic composition, by computer, providing a complete genomic DNA sequence for the organism and determining the effect of changes in connectrons due to application of a given exogenous stimulus to the genome.

Claims 28 - 37 are dependent from claim 20 and stand or fall with that claim.

CONCLUSION

In conclusion, appellant submits that Mr. Oberthaler was correct in stating:

> The specification provides a detailed roadmap for practicing the invention by one skilled in the art. Referring specifically to the specification and drawings, the introduction at pages 1 - 3 provides a basic description of connectron structure. Figures 1 - 3 are taken from the text by Alberts et al. entitled "The Molecular Biology of the Cell." Pages 3 - 25. Pages 26 - 36 provides a detailed description of a connectron structure. Page 31, the detailed description of the invention, provides a descriptive analysis of the flow diagrams utilized in the computer analysis of connectrons in any given genome.
>
> Ten samples of connectrons found by computer mediation are set out in the specification. Pages 39 - 56 give an example of a prokaryote connectron - E. coli. I have considered this example as well as all examples given against the backdrop of the Examiner's contention that the description lacks clear evidence of the connectron symmetries as related to gene expression and in my opinion that the skilled practitioner would not have any difficulty in practicing the invention from these descriptions for the following reasons:
>
> (1) The flowcharting conventions used are typical of these used to present computer algorithms. Together, they provide all the detail required for a complete implementation.
>
> (2) A wide variety of computer languages could be used to implement the algorithm. Any procedural third generation language could be used.
>
> (3) These skills are well within the competence of even journeyman programmers using languages such as Fortran, Cobol, PL-I, ALGOL< Pascal. etc, as well as more modern languages such as C, C++, etc.
>
> (4) Computers with the necessary performance and capacity are readily available for an amount that is well within the reach of many home budgets, let alone the

resources available to corporations and research institutions.

Appellant respectfully submits that the Examiner erred in finally rejecting claims 20 - 37 and should be reversed.

Respectfully submitted,

Jim Zegeer, Reg. No. 18,957
Attorney for Appellant

Attachment: CLAIMS APPENDIX
EVIDENCE APPENDIX

Suite 108
801 North Pitt Street
Alexandria, VA 22314
Telephone: 703-684-8333

Date: August 5, 2005

In the event this paper is deemed not timely filed, the applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to Deposit Account No. 26-0090 along with any other additional fees which may be required with respect to this paper.

(viii) CLAIMS APPENDIX

20. A computer mediated method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, one or more pairs of first and second non-adjacent DNA sequences which could bind to one RNA molecule such that a first RNA sequence in that RNA molecule can bind to a first non-adjacent DNA sequence and a second RNA sequence in that RNA molecule can bind to a second non-adjacent DNA sequence.

21. A computer mediated method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising, by computer, detecting, by computer, changes in connectron behavior in the genome as a function of changes in the sequence of the genome.

22. A computer mediated method of detecting changes in expression of different gene collections in a genome, comprising: by computer, detecting changes in expression of different gene collections in a genome that result in changes in the level of connectron control sequences caused by an exogenous stimulus.

23. A computer mediated method of detecting, by computer, where and when new genes have been integrated into a host genome comprising detecting an operable link between a newly introduced gene and a preexisting connectron behavior in said host genome.

24. A computer mediated method of detecting the expression effect of different gene collections in a given host genome, comprising: by computer, detecting the effect of connectrons on transcription.

25. A computer mediated method of changing the expression of different gene collections in a genome comprising modifying, by a computer, identification of connectron organization.

26. A method of detecting connectron control and target sequences in a given genome comprising:

by computer, determining the base composition of said genome, determining one or more sites of control sequence organization, and/or
determining one or more sites of target application.

27. A computer mediated method of determining the response of a cell in any tissue to changes in the cell's environment and/or genetic composition comprising: by computer, providing a complete genomic DNA sequence for the organism and determining the effect of changes in connectrons due to application of a given exogenous stimulus to the genome.

28. Using the method as defined in claim 20, in prokaryotes, archea, single-celled eukaryotes and multi-celled eukaryotes, where the DNA sequence and the RNA molecule can form a tetradic relationship such that T1=C1 and T2=C2 where T1 and T2 are DNA sequences 20 or more bases in length, where the C1 sequence is adjacent to the C2 sequence, where the T1 and T2 sequences are on the same chromosome, and where the C1/C2 sequences are on the same chromosome as T1 and T2 or where the C1/C2 sequences are on a chromosome different from T1 and T2, wherein:

C1 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C2 sequence must occur in the same chromosome as the C1 sequence,

C2 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C1 sequence must occur in the same chromosome as the C2 sequence,

C1/C2 - any positive or negative strand DNA sequence of 40 or more bases such that the C1 sequence is adjacent to the C2 sequence,

T1 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T2 sequence, the T1 and T2 sequences must be between about 1kb and 105kb apart, and

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1 sequence, the T2 or T1 sequences must be between about 1kb and 105kb apart.

29. Using the method as defined in claim 20, in prokaryotes, archea, single-celled eukaryotes and multi-celled eukaryotes, where the DNA sequences and the RNA molecule function as a connectron that permits many different C1/C2 short loops to control the existence of a T1-T2 long loop and wherein said C1/C2 short lops can be on the same chromosome or on different chromosomes from the T1-T2 long loop, wherein:

C1 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C2 sequence must occur in the same chromosome as the C1 sequence,

C2 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C1 sequence must occur in the same chromosome as the C2 sequence,

C1/C2 - any positive or negative strand DNA sequence of 540 or more bases such that the C1 sequence is adjacent to the C2 sequence,

T1 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T2 sequence, the T1 and T2 sequences must be between about 1kb and 105kb apart, and

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1 sequence, the T2 or T1 sequences must be between about 1kb and 105kb apart.

30. Using the method as defined in claim 20, in prokaryotes, archea, single-celled eukaryotes and multi-celled eukaryotes, where the DNA sequences and the RNA molecule function as a connectron that permits one C1/C2 short loop to control the existence of many T1-T2 long loops, the C1/C2 short loop can be on the same chromosome or on different chromosomes from the T1-T2 long loops, wherein:

C1 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C2 sequence must occur in the same chromosome as the C1 sequence,

C2 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C1 sequence must occur in the same chromosome as the C2 sequence,

C1/C2 - any positive or negative strand DNA sequence of 40 or more bases such that the C1 sequence is adjacent to the C2 sequence,

T1 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T2 sequence, the T1 and T2 sequences must be between about 1kb and 105kb apart, and

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1 sequence, the T2 or T1 sequences must be between about 1kb and 105kb apart.

31. Using the method as defined in claim 20, where the DNA sequences and the RNA molecule function as a connectron between prokaryotes and their plasmids and wherein said connectron implements a control mechanism between the two genomes that makes it possible from them to form a symbiotic relationship, and in the case of D. radiodurans the relationship is not symmetric, and the D. radiodurans genome sends C1/C2 short loops to the MP1 plasmid, wherein:

C1 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C2 sequence must occur in the same chromosome as the C1 sequence,

C2 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C1 sequence must occur in the same chromosome as the C2 sequence,

C1/C2 - any positive or negative strand DNA sequence of 40 or more bases such that the C1 sequence is adjacent to the C2 sequence,

T1 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T2

sequence, the T1 and T2 sequences must be between about 1kb and 105kb apart, and

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1 sequence, the T2 or T1 sequences must be between about 1kb and 105kb apart.

32. Using the method as defined in claim 20, where the DNA sequences and the RNA molecule function as a connectron that exist in a plant or a higher animal.

33. Using the method as defined in claim 20, in prokaryotes, archea, single-celled eukaryotes and multi-celled eukaryotes, where the DNA sequences and the RNA molecule function as a connectron that permits one C1/C2 short loop to control the existence of one or more T1-T2 long loops without being subject to any expression controls other than those of the gene to which the C1/C2 is 3'UTR, wherein:

C1 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C2 sequence must occur in the same chromosome as the C1 sequence,

C2 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C1 sequence must occur in the same chromosome as the C2 sequence,

C1/C2 - any positive or negative strand DNA sequence of 40 or more bases such that the C1 sequence is adjacent to the C2 sequence,

T1 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T2

sequence, the T1 and T2 sequences must be between about 1kb and 105kb apart,

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1 sequence, the T2 or T1 sequences must be between about 1kb and 105kb apart, and

3'UTR - untranslated 3' end of an mRNA is beyond the end of the last exon, a stop codon in the mRNA causes the ribosome to stop the translation of mRNA into protein.

34. Using the method as defined in claim 20, in prokaryotes, archea, single-celled eukaryotes and multi-celled eukaryotes, where the DNA sequences and the RNA molecule function as a connectron that permits one C1/C2 short loop to control the existence of one or more T1-T2 long loops such that this C1/C2 short loop is itself subject to expression control by another T1-T2 long loop which surrounds it, wherein:

C1 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C2 sequence must occur in the same chromosome as the C1 sequence,

C2 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C1 sequence must occur in the same chromosome as the C2 sequence,

C1/C2 - any positive or negative strand DNA sequence of 40 or more bases such that the C1 sequence is adjacent to the C2 sequence,

T1 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T2

sequence, the T1 and T2 sequences must be between about 1kb and 105kb apart, and

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1 sequence, the T2 or T1 sequences must be between about 1kb and 105kb apart.

35. Using the method as defined in claim 20, in prokaryotes, archea, single-celled eukaryotes and multi-celled eukaryotes, where the DNA sequences and the RNA molecule function as a connectron that permits one C1/C2 short loop to control the existence of the T1-T2 long loop that surrounds it, wherein:

C1 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C2 sequence must occur in the same chromosome as the C1 sequence,

C2 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C1 sequence must occur in the same chromosome as the C2 sequence,

C1/C2 - any positive or negative strand DNA sequence of 50 or more bases such that the C1 sequence is adjacent to the C2 sequence,

T1 sequence - any positive or negative strand DNA sequence of 20bases or more that is on the same chromosome as the T2 sequence, the T1 and T2 sequences must be between about 1kb and 105kb apart, and

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1

sequence, the T2 or T1 sequences must be between about 1kb and 105kb apart.

36. Using the method as defined in claim 20, where the DNA sequences and the RNA molecule function as a connectron that does not have any genes within the T1-T2 long loop, wherein:

T1 sequence is any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T2 sequence, and

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1 sequence, and the T2 or T1 sequences must be between about 1kb and 105kb apart.

37. Using the method as defined in claim 20, where the DNA sequences and the RNA molecule function as a geneless connectron where one C1/C2 short loop controls the existence of many geneless T1-T2 long loops, wherein:

C1 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C2 sequence must occur in the same chromosome as the C1 sequence,

C2 sequence - any positive or negative strand DNA sequence of 20 bases or more, the C1 sequence must occur in the same chromosome as the C2 sequence,

C1/C2 - any positive or negative strand DNA sequence of 40 or more bases such that the C1 sequence is adjacent to the C2 sequence,

T1 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T2 sequence, the T1 and T2 sequences must be between about 1kb and 105kb apart, and

T2 sequence - any positive or negative strand DNA sequence of 20 bases or more that is on the same chromosome as the T1 sequence, the T2 or T1 sequences must be between about 1kb and 105kb apart.

(ix). EVIDENCE APPENDIX

1. Declaration Under 37 C.F.R. §1.132 (Richard W. Pastor)
2. Declaration Under 37 C.F.R. §1.132 (James V. Oberthaler)

The above two Declarations were filed in the USPTO with applicant's response on June 9, 2003.

See the Examiner's rejection in the Office Action mailed October 8, 2003 at page 4, paragraph 10.

(x). RELATED PROCEEDINGS APPENDIX

There are no proceedings as mentioned in section (i) above, and accordingly no decisions rendered.

#15
Appeal

Atty. Docket No.: 3124-4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Richard J. Feldmann

Serial No. 09/866,925 Group Art Unit 1645

Filed: May 30, 2001 Examiner John S. Brusca

For: ALGORITHMIC DETERMINATION OF FLANKING DNA SEQUENCES THAT CONTROL THE EXPRESSION OF SETS OF GENES IN PROKARYOTIC, ARCHEA AND EUKARYOTIC GENOMES

DECLARATION UNDER 37 C.F.R. 1.132

Hon. Commissioner of Patents & Trademarks
Washington, D. C. 20231

Sir:

I, James V. Oberthaler, whose address is 7701 Woodmont Avenue, Apt. 406, Bethesda MD, 20814, declare as follows:

1. I received a BS degree in Mathematics from the College of the Holy Cross. I also did graduate work in Mathematics at the University of Maryland and the American University, completing all requirements for an MA in Mathematics except the dissertation. I hold a Masters degree in Business Administration from Southern Illinois University at Edwardsville, IL. My work experience includes over 40 years of software design and engineering and management of these activities. My relevant experience is described briefly in the Curriculum Vitae that accompanies this letter. I currently serve as Principal Research Analyst, under contract to the National Cancer

Institute Center for Bioinformatics.

2. I have read the patent specification for application Serial No. 09/866,925 as filed in the United States Patent & Trademark Office on May 30, 2001 for "ALGORITHMIC DETERMINATION OF FLANKING DNA SEQUENCES THAT CONTROL THE EXPRESSION OF SETS OF GENES IN PROKARYOTIC, ARCHEA AND EUKARYOTIC GENOMES." I read the amended claims submitted October 30, 2002, and I have read the amended claims submitted with the amendment accompanying this Declaration. I have read the official communication from the U.S. Patent & Trademark Office dated January 8, 2003. I have considered all of the claims.

3. I wish first to direct my comments to claims 20 - 27 which, I have been advised, are the broadest claims in the application. I have been also advised that claims 28 - 37 are all dependent from claim 20 and, hence, include the limitations of claim 20.

Claims 20 - 27 are as follows:

20. A method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, one or more pairs of non-adjacent DNA sequences to which are bound one RNA molecule comprising of two RNA sequences.

21. A method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, changes in connectron behavior in the genome as a function of changes in the sequence of the genome.

22. A method of modifying, by computer, the expression of different gene collections in a genome, comprising detecting changes in connectron behavior that results in changes in the level of connectron control sequences caused by an exogenous stimulus.

23. A method of detecting, by computer, where and when new genes have been integrated into a host genome comprising detecting the operable link between the newly introduced gene and the existing connectron behavior in said host genome.

24. A method of detecting, by computer, the expression effect of different gene collections in a given host genome, comprising detecting the transacting behavior of connectrons between the chromosomes thereof.

25. A method of modifying a given genome comprising modifying, by computer, the connectron organization therein.

26. A method of detecting, by computer, connectron control and target sequences in a given genome comprising:

determining the base composition of said genome,

determining one or more sites of control sequence organization, and/or

determining one or more sites of target application.

27. A method of determining, by computer, the response of a cell in any tissue to changes in the cell's environment and/or genetic composition comprising providing a complete genomic DNA sequence for the organism and determining the effect of changes in connectrons due to application of a given exogenous stimulus to the genome.

4. It should be noted that all of the claims, including the dependent claims, are directed to a tetradic relationship between two specific adjacent RNA single-stranded sequences (called C1 and C2 for control sequence 1 and control sequence 2), which interact with two distant double-stranded DNA sequences (called T1 and T2 for target sequence 1 and target sequence 2). Claim 20 refers to a computer algorithm for identifying DNA sequences that control the expression of different collections of genes in a genome by identifying one or more pairs of non-adjacent DNA sequences to which are bound one RNA molecule containing two RNA sequences.

5. Referring to pages 5 and 6 of the Examiner's action and in reference to subparagraphs a) through h), I wish to state the following:

In subpagraph a), the Examiner first states that in order to practice the claimed invention, one skilled in the art must identify and use a connectron to predict the relation of gene expression. Keeping in mind that the claims under consideration are directed to computer mediated methods of analysis of connectron sequences, I disagree with the Examiner's conclusion for the following reasons:

(1) Claim 20 asserts that this patent application provides a mechanism (i.e., a computer algorithm) whereby one skilled in the art (i.e., a journeyman, molecular biologist, bioinformatician, or computer programmer who understands the storage format, content and use of readily available bioinformatics resources) can write software, following the algorithm, that will analyze the DNA sequence of an organism to identify DNA sequences (called C1, C2, T1 and T2 in the description of the algorithm) meeting specific criteria set forth in the description. And, further, that the identified sequences behave in such a way that when the control sequence containing C1 and C2 is transcribed into RNA, the RNA will seek out and bind to the target sequence (C1 binding to T1 and C2

binding to T2) to achieve the effect that the entire DNA sequence beginning with T1 and ending with T2 is shielded from transcription

(2) The software, implemented following the algorithm and set to work on standard, readily available genome sequences, will identify the collection of DNA and RNA sequences making up connectrons as defined in the patent application without any need for understanding by or help from the computer programmer.

Further, in subparagraph b), the Examiner states that the description provides guidance to identify connectron symmetries in genomic sequences, and I agree. However, the Examiner also contends that the description does not provide detailed guidance to use identified connectron symmetries to predict an effect on gene expression, and with respect to this contingent I disagree for same reasons stated in paragraphs (1) and (2) above.

In subparagraph c), the Examiner contends that the description provides working examples of identification of connectron symmetries in genomic sequences, and I agree. See pages 37 and 38 of the specification for a listing of the examples, and pages 39 - 188 for detailed expositions of sample uses of the algorithm. The Examiner

further contends that the description does not provide working examples of using identified connectron symmetries to predict effects on gene expression.

I disagree. On the contrary, this is exactly what the examples provide. As explained in the introduction and in the definitions provided, (particularly, the definitions of Possible Connectron and Hierarchy of Connectron Action) each connectron control sequence C1-C2 will, when transcribed into RNA, seek out and bind to its target sequence T1-T2, thereby shielding the DNA between T1 and T2 from transcription. Since the shielded DNA sequence will not be transcribed, any genes in the span between T1 and T2 will not be expressed as proteins for as long as the C1-C2 sequence remains bound to T1-T2. Similarly, any additional C1-C2 sequences in the span between T1 and T2 will also remain inactive during this time period, and therefore the inhibitory effect they otherwise would have exerted on their target sequences will be suppressed during this time period. Granted that the full, cascading sequence of transcription/expression and sequestration that would result from each of the examples discussed is not presented, the principles are given that would enable anyone who understands the mechanism, as explained in the application, to follow the effects as deeply as he or she desires.

In subparagraph d), the Examiner states that the nature of the invention, gene expression control, is complex. I agree for the reasons stated in the preceding paragraph and for the even more fundamental reason that the molecular-biological processes of even the simplest cell are very complex. Life is very complex: a fully formed organism with incredibly complicated biological activities develops from a single cell and lives a full lifetime by interacting in countless ways with its external environment. It would often be impossible to enumerate to completion all the effects that even a single connectron turning on or off would cause. Some cells would cycle through millions of possible states before repeating one. The only reasonable presentation of these effects is to give the principles that apply, and this has been done clearly and completely in the application.

In subparagraph e), the Examiner asserts that the prior art does not show connectrons; and for the purposes of this Declaration, I am assuming that the connectrons have the definition given above. I agree with the Examiner's contention. Mattick does not show connectrons as defined in the instant specification. It is my understanding and belief that the connectron invention disclosed in

the present application was made by the inventor, Richard J. Feldmann.

In subparagraph f), the Examiner contends that the skill of the art of gene expression is high, and I agree.

In subparagraph g), the Examiner contends that the predictability of the relationship of connectron symmetries and gene expression is unknown in the prior art, and I agree. Although I do not present myself as an expert in genetics or molecular biology, it is clear from the nature of the publications appearing at the time this letter is written that laboratory researchers are only now beginning to encounter, case by case, the effects disclosed by Mr. Feldmann's fully-formed connectron invention. To the best of my knowledge, these investigators are discovering individual applications of the invention, but no one except Mr. Feldmann has yet disclosed the overarching theory and its implications.

In subparagraph h), the Examiner contends that the claims are broad in that they are drawn to identification of connectron symmetries whose relationship to gene expression is not established. While I am not cognizant of the legal terms or definitions for the

breadth of claims, my understanding of the breadth of method claim 20, for example, is that it requires detecting a DNA sequence that controls the expression of different collections of genes in a genome comprising detecting, by computer, one or more pairs of non-adjacent DNA sequences to which are bound RNA molecule comprising two RNA sequences.

Claim 21 is directed to a method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, changes in connectron behavior in the genome as a function of changes in the sequence of the genome.

Claim 25 recites the method of changing a given genome comprising modifying, by computer, the connectron organization therein.

Claim 26 is directed to:

a method of detecting, by computer, connectron control and target sequences in a given genome comprising:

determining the base composition of said

genome,

determining one or more sites of control sequence organization and/or

determining one or more sites of target application.

I agree that the skilled practitioner would turn to the description and drawings provided in the application for guidance in using the claimed invention. The specification provides a detailed roadmap for practicing the invention by one skilled in the art. Referring specifically to the specification and drawings, the introduction at pages 1 - 3 provides a basic description of connectron structure. Figures 1 - 3 are taken from the text by Alberts et al. entitled "The Molecular Biology of the Cell." Pages 3 - 25. Pages 26 - 36 provides a detailed description of a connectron structure. Page 31, the detailed description of the invention, provides a descriptive analysis of the flow diagrams utilized in the computer analysis of connectrons in any given genome.

Ten samples of connectrons found by computer mediation are set out in the specification. Pages 39 - 56 give an example of a prokaryote connectron - E. coli. I have considered this example as

well as all examples given against the backdrop of the Examiner's contention that the description lacks clear evidence of the connectron symmetries as related to gene expression and in my opinion that the skilled practitioner would not have any difficulty in practicing the invention from these descriptions for the following reasons:

(1) The flowcharting conventions used are typical of those used to present computer algorithms. Together, they provide all the detail required for a complete implementation.

(2) A wide variety of computer languages could be used to implement the algorithm. Any procedural third generation language could be used.

(3) These skills are well within the competence of even journeyman programmers using languages such as Fortran, Cobol, PL-I, ALGOL< Pascal, etc., as well as more modern languages such as C, C++, etc.

(4) Computers with the necessary performance and capacity are readily available for an amount that is well within the reach of

many home budgets, let alone the resources available to corporations and research institutions.

Finally, in conclusion, I disagree with the Examiner's contention that the trial and error experimentation required to practice the invention amounts to undue experimentation for the following reasons:

(1) As stated earlier, the algorithms presented are straightforward and complete.

(2) No experimentation whatsoever is required. Implementing the algorithms is a routine exercise in program design, coding and debugging. Running them is simply a matter of obtaining the organism-specific genomes and allowing the computer programs to go to work on them.

(3) The only part of the activity that could conceivably be referred to as "experimenting" is the investigation into available bioinformatics resources, such as the syntax and semantics of the resources provided by, for example, that National Library of Medicine's National Center for Biotechnology Information (NCBI). It is clear that in this context, having a ready understanding of this

information is a reasonable characteristic of one who could be called "skilled in the art."

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 6/5/2003

James V. Oberthaler
(Signature)

Name: JAMES V. OBERTHALER

Atty. Docket No.: 3124-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#15/Dec. w/Spec.

In re application of
Richard J. Feldmann
Serial No. 09/866,925 Group Art Unit 1645
Filed: May 30, 2001 Examiner John S. Brusca
For: ALGORITHMIC DETERMINATION OF FLANKING DNA SEQUENCES THAT CONTROL THE EXPRESSION OF SETS OF GENES IN PROKARYOTIC, ARCHEA AND EUKARYOTIC GENOMES

DECLARATION UNDER 37 C.F.R. 1.132

Hon. Commissioner of Patents & Trademarks
Washington, D. C. 20231

Sir:

I, Richard W. Pastor, whose address is Laboratory of Biophysics, Center for Biologics Evaluation and Research, US Food and Drug Administration, 1401 Rockville Pike, Rockville MD, 20852-1448, declare as follows:

1. I received a Ph.D. degree in Biophysics from Harvard University. I also hold a MS degree in Chemistry from Syracuse University. My work experience includes 19 years (since Ph.D.) of research related to the computer simulation of biological systems, as well as supervision of related activities. I currently serve as Chief of the Laboratory of Biophysics in at the Center for Biologics Evaluation and Research, US Food and Drug Administration.

2. I have read the patent specification for application Serial No. 09/866,925 as filed in the United States Patent &

Trademark Office on May 30, 2001 for "ALGORITHMIC DETERMINATION OF FLANKING DNA SEQUENCES THAT CONTROL THE EXPRESSION OF SETS OF GENES IN PROKARYOTIC, ARCHEA AND EUKARYOTIC GENOMES." I read the amended claims submitted October 30, 2002, [and I have read the amended claims submitted with the amendment accompanying this Declaration]. I have read the official communication from the U.S. Patent & Trademark Office dated January 8, 2003. I have considered all of the claims.

3. I wish first to direct my comments to claims 20 - 27 which, I have been advised, are the broadest claims in the application. I have been also advised that claims 28 - 37 are all dependent from claim 20 and hence I am advised include the limitations of claim 20.

Claims 20 - 27 are as follows:

20. A method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, one or more pairs of non-adjacent DNA sequences to which are bound one RNA molecule comprising of two RNA sequences.

21. A method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, changes in connectron behavior in the genome as a function of changes in the sequence of the genome.

22. A method of modifying, by computer, the expression of different gene collections in a genome, comprising detecting changes in connectron behavior that results in changes in the level of connectron control sequences caused by an exogenous stimulus.

23. A method of detecting, by computer, where and when new genes have been integrated into a host genome comprising detecting the operable link between the newly introduced gene and the existing connectron behavior in said host genome.

24. A method of detecting, by computer, the expression effect of different gene collections in a given host genome, comprising detecting the transacting behavior of connectrons between the chromosomes thereof.

25. A method of modifying a given genome comprising modifying, by computer, the connectron organization therein.

26. A method of detecting, by computer, connectron control and target sequences in a given genome comprising:

determining the base composition of said genome,
determining one or more sites of control sequence organization, and/or
determining one or more sites of target application.

27. A method of determining, by computer, the response of a cell in any tissue to changes in the cell's environment and/or genetic composition comprising providing a complete genomic DNA sequence for the organism and determining the effect of changes in connectrons due to application of a given exogenous stimulus to the genome.

4. It should be noted that all of the claims, including the dependent claims, are directed to a tetradic relationship between two specific adjacent RNA single-stranded sequences (called C1 and C2 for control sequence 1 and control sequence 2) interact with two distant double-stranded DNA sequences (called T1 and T2 for target sequence 1 and target sequence 2). Claim 20 recites a method of identifying DNA sequences that control the expression of different collections of genes in a genome comprising detecting, by computer, one or more pairs of non-adjacent DNA sequences to which are bound one RNA molecule comprising of two RNA sequences.

5. I wish to state the following referring to pages 5 and 6

of the Examiner's action and in reference to subparagraphs a) through h):

In subpagraph a), the Examiner first states that in order to practice the claimed invention, one skilled in the art must identify and use a connectron to predict the relation of gene expression. Keeping in mind that the claims under consideration are directed to computer mediated methods of analysis of connectron sequences, I disagree with the Examiner's conclusion that there would be an unpredictable amount of experimentation required to practice the claimed invention.

The skilled practitioner would turn to the instant description and drawings for guidance in using the claimed invention. The specification provides a detailed roadmap for practicing the invention by one skilled in the art. Referring specifically to the specification and drawings, the introduction at pages 1 - 3 provides a basic description of connectron structure. Figures 1 - 3 are taken from the text by Alberts et al. entitled "The Molecular Biology of the Cell." Pages 3 - 25. Pages 26 - 36 provides a detailed description of a connectron structure. Page 31, the detailed description of the invention, provides a descriptive analysis of the flow diagrams utilized in the computer analysis of connectrons in any given genome. Additionally, ten samples of connectrons found by computer mediation are set out in the specification. Pages 39 - 56 give an example of a prokaryote connectron - E. coli. Hence, the algorithm is clearly defined and

could be programmed by a skilled scientist. In this sense, the amount of experimentation is quite predictable.

I agree that the nature of the invention, gene control, is complex, and that prior art does not discuss connectron symmetries; i.e., tt is my understanding and belief that the connectron invention disclosed in the instant application was made by the inventor, Richard J. Feldmann.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 6/5/03 _____

(Signature)

Name: Richard W Pastor

June, 2003

CURRICULUM VITAE

Richard W. Pastor, Ph.D.

Address: Biophysics Laboratory
Center for Biologics Evaluation and Research, FDA
1401 Rockville Pike, Rockville MD 20852-1448
rwpastor@fda.cber.fda.gov

Date of Birth: June 21, 1951

Citizenship: United States

Education:

1984 Ph.D. Harvard University, Biophysics
Dissertation Title: *Topics in Stochastic Dynamics of Polymers.* Preceptor: Martin Karplus

1977 M.S. Syracuse University, Chemistry
Thesis Title: *Surface Tension Calculations for Molten Salts: Critique and Modification of the Kirkwood-Buff Model.*
Preceptor: Jerry Goodisman

1973 B.A. Hamilton College, Major in Philosophy

Employment:

1996-Present Chief, Biophysics Laboratory, CBER/FDA

1998 Acting Chief, Laboratory of Immunobiochemistry, CBER/FDA

1990-1996 Research Chemist, Biophysics Lab, CBER/FDA

1984-1990 Senior Staff Fellow, Biophysics Lab, CBER/FDA

1984 Staff Fellow, Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

Awards:

1997 *Center Director's Public Health Achievement Award*
Center for Biologics Evaluation and Research

1996 *Scientific Achievement - Senior Investigator*
Center for Biologics Evaluation and Research

1996 *Excellence in Science by a Group*
Food and Drug Administration

1977 *Teaching Assistant of the Year*
Department of Chemistry, Syracuse University

Research Area: The application of computer simulations and statistical mechanics to biophysics, with emphasis on membranes.

Richard W. Pastor, Ph.D.

Teaching:

1994 Adjunct Professor, George Mason University
Physical Biochemistry

1978-1980 Teaching Fellow, Harvard University
Physical Biochemistry and Introductory Biochemistry

1975-1977 Teaching Fellow, Syracuse University
General Freshman and Honors Freshman Chemistry

Publications

1. Resonance Raman Studies of Macrocyclic Complexes. 1. Structural and Electronic Effects in Synthetic Metal (II) Porphrin Analogues. W.H. Woodruff, R.W. Pastor and J.C. Dabrowiak, *J. Am. Chem. Soc.* 98, 7999-8006 (1976).

2. Resonance Raman Studies of Macrocyclic Complexes. 2. Antiresonance and Selective Intensity Enhancement in Synthetic Metal (II) Porphrin Analogues, L.A. Nafie, R.W. Pastor, J.C. Dabrowiak and W.H. Woodruff, *J. Am. Chem. Soc.* 98, 8007-8014 (1976).

3. Surface Tension Calculations for Molten Salts: Critique and Modification of the Kirkwood-Buff Model, R.W. Pastor and J. Goodisman, *J. Chem. Phys.* 68, 3654-3666 (1978).

4. A Model for the Surface of a Molten Salt, J. Goodisman and R.W. Pastor, *J. Phys. Chem.* 82, 2078-2081 (1978).

5. A Recognition Site in Synthetic Helical Oligonucleotides for Monoclonal Anti-Native DNA Autoantibody, David Stollar, Gerald Zon and Richard W. Pastor, *Proc. Natl. Acad. Sci. USA* 83, 4469-2273 (1986).

6. Local Sequence Patterns of Hydrophobicity and Solvent Accessibility in Soluble Globular Proteins, David. J. Lipman, Richard W. Pastor and B. Lee, *Biopolymers* 26, 17-26 (1987).

7. A Theoretically Determined Three-Dimensional Structure for the Repeating Tetrapeptide Unit of the Circumsporozoite Coat Protein of the Malaria Parasite Plasmodium falciparum, Bernard R. Brooks, Richard W. Pastor, Frederick W. Carson, *Proc. Natl. Acad. Sci. USA* 84, 4470-4474 (1987).

8. The Parametrization of the Friction Constant for Stochastic Simulations of Polymers, Richard W. Pastor and Martin Karplus, *J. Phys. Chem.* 92, 2636-2641 (1988).

9. Frictional Models for Stochastic Simulations of Proteins, Richard M. Venable and Richard W. Pastor, *Biopolymers* 27, 1001-1014 (1988).

10. Brownian Dynamics Simulation of a Lipid Chain in a Membrane Bilayer, Richard W. Pastor, Richard M. Venable and Martin Karplus, *J. Chem. Phys.* 89, 1112-1127 (1988).

11. A Simulation Based Model of NMR T_1 Relaxation in Lipid Bilayer Vesicles, Richard W. Pastor, Richard M. Venable, Martin Karplus, and Attila Szabo, *J. Chem. Phys.* 89, 1128-1140 (1988).

Richard W. Pastor, Ph.D.

Publications (cont.)

12. An Analysis of the Accuracy of Langevin and Molecular Dynamics Algorithms, Richard W. Pastor, Bernard R. Brooks and Attila Szabo, *Mol. Phys.* 65, 1409-1419 (1988).

13. Theoretically Determined Three-Dimensional Structures for Amphipathic Segments of the HIV-1 gp41 Envelope Protein, Richard M. Venable, Richard W. Pastor, Bernard R. Brooks and Frederick W. Carson, *AIDS Research and Human Retroviruses* 5, 7-21 (1989).

14. Anisotropic Bead Models for Molecular Hydrodynamics, Richard W. Pastor and Robert Zwanzig, *J. Chem. Phys.* 90, 5729-5734 (1989).

15. Inertial Effects in Butane Stochastic Dynamics, Richard W. Pastor and Martin Karplus, *J. Chem. Phys.* 91, 211-218 (1989).

16. Determination of Chain Conformations in the Membrane Interior by Brownian Dynamics Simulations, Richard W. Pastor, in *Molecular Description of Biological Membrane Components by Computer Aided Conformational Analysis*, Vol. I, (ed. R. Brasseur, CRC Press, Boca Raton, 1990), pp. 171-201.

17. Model for the Structure of the Lipid Bilayer, Richard W. Pastor, Richard M. Venable and Martin Karplus, *Proc. Natl. Acad. Sci. USA* 88, 892-896 (1991).

18. Mean Field Stochastic Boundary Molecular Dynamics Simulation of a Phospholipid in a Membrane, Hans De Loof, Stephen C. Harvey, Jere P. Segrest and Richard W. Pastor, *Biochemistry* 30, 2099-2113 (1991).

19. Molecular Dynamics Simulation of Methyl Group Relaxation in Water, Goran Widmalm, Richard W. Pastor and T.E. Bull, *J. Chem. Phys.* 94, 4097-4098 (1991).

20. Analyses of Statistical Errors in Dynamics Simulations, Richard W. Pastor, in *Proteins: Structure, Dynamics, Design* (ed. V. Renugopalakrishnan, P.R. Carey, I.C.P. Smith, S.G. Huang and A.C. Storer, ESCOM Science Publishers, The Netherlands, 1991), pp. 229-233.

21. Synexin: Molecular Mechanism of Calcium-Dependent Membrane Fusion and Voltage-Dependent Calcium Channel Activity, Harvey B. Pollard, Eduardo Rojas, Richard W. Pastor, Eduardo M. Rojas, H. Robert Guy, and A. Lee Burns, *Ann. New York Acad. Sci.* 635, 328-351 (1991).

22. Langevin Dynamics of Peptides: the Frictional Dependence of Isomerization Rates of N-Acetylalanyl-N'-Methylamide, Richard J. Loncharich, Bernard R. Brooks and Richard W. Pastor, *Biopolymers* 32, 523-535 (1992).

23. Backbone Dynamics of Calmodulin Studied by ^{15}N Relaxation Using Inverse Detected Two-Dimensional NMR Spectroscopy: The Central Helix is Flexible, Gaetano Barbato, Mitsuhito Ikura, Lewis E. Kay, Richard W. Pastor and Ad Bax, *Biochemistry* 31, 5269-5278 (1992).

24. Conformational States of a TT Mismatch from Molecular Dynamics Simulation of d(CGCGATTCGCG), Richard M. Venable, Goran Widmalm, Bernard R. Brooks, William Egan and Richard W. Pastor, *Biopolymers* 32, 783-794 (1992).

Richard W. Pastor, Ph.D.

Publications (cont.)

25. A Comparison of Langevin and Molecular Dynamics Simulations: Equilibrium and Dynamics of Ethylene Glycol in Water, Goran Widmalm and Richard W. Pastor, *J. Chem. Soc. Faraday Trans.* 88, 1747-1754 (1992).

26. Langevin Dynamics of a Linear Rotor in a Maier-Saupe Potential: Kramers Turnover of the Flipping Rate, Richard W. Pastor and Attila Szabo, *J. Chem. Phys.* 97, 5098-5100 (1992).

27. Positional Time Correlation Function for One-Dimensional Systems with Barrier Crossing: Memory Function Corrections to the Optimized Ronse-Zimm Approximation, Angelo Perico, Roberto Pratolongo, Karl F. Freed, Richard W. Pastor and Attila Szabo, *J. Chem. Phys.* 98, 564-573 (1993).

28. Molecular Dynamics Simulations of a Lipid Bilayer and of Hexadecane: An Investigation of Membrane Fluidity, Richard M. Venable, Yuhong Zhang, Barry J. Hardy and Richard W. Pastor, *Science* 262, 223-226 (1993).

29. Molecular and Stochastic Dynamics Simulation of Lipid Membranes, Richard W. Pastor and Richard M. Venable, in *Computer Simulation of Biomolecular Systems: theoretical and experimental applications* (ed. Wilfred F. van Gunsteren, Paul K. Weiner and Anthony K. Wilkinson, ESCOM Science Publishers, Leiden, 1993), pp. 443-463.

30. Conformational Sampling of Hydrocarbon and Lipid Chains in an Ordering Potential, Barry J. Hardy and Richard W. Pastor, *J. Comput. Chem.* 15, 208-226 (1994).

31. A Comparison of Methods for Computing Transition Rates from Molecular Dynamics Simulation, Yuhong Zhang and Richard W. Pastor, *Mol. Sim.* 13, 25-38 (1994).

32. Techniques and Applications of Langevin Dynamics Simulations, Richard W. Pastor, in *The Molecular Dynamics of Liquid Crystals* (eds. G.R. Luckhurst and C.A. Veracini, Kluwer Academic Publishers, The Netherlands, 1994), pp. 85-138.

33. Molecular Dynamics and Monte Carlo Simulations of Lipid Bilayers, Richard W. Pastor, *Current Opinion in Structural Biology* 4, 486-492 (1994).

34. Method For Characterizing Transition Concertedness From Polymer Dynamics Computer Simulations, Michael L. Brown, Richard M. Venable and Richard W. Pastor, *Biopolymers* 35, 31-46 (1995).

35. Constant Pressure Molecular Dynamics Simulation: The Langevin Piston Method, Scott E. Feller, Yuhong Zhang, Richard W. Pastor and Bernard R. Brooks, *J. Chem. Phys.* 103, 4613-4621 (1995).

36. Computer Simulation of Liquid/Liquid Interfaces. I. Theory and Application to Octane/Water, Yuhong Zhang, Scott E. Feller, Bernard R. Brooks and Richard W. Pastor, *J. Chem. Phys.* 103, 10252-10266 (1995).

Richard W. Pastor, Ph.D.

Publications (cont.)

37. Computer Simulation of Liquid/Liquid Interfaces. II. Surface Tension-Area Dependence of a Bilayer and Monolayer, Scott E. Feller, Yuhong Zhang and Richard W. Pastor *J. Chem. Phys.* 103, 10267-10276 (1995).

38. Rotational Diffusion Anisotropy of Human Ubiquitin from ^{15}N NMR Relaxation, Nico Tjandra, Scott E. Feller, Richard W. Pastor and Ad Bax, *J. Am. Chem. Soc.* 117, 12562-12566 (1995).

39. Molecular Dynamics Simulations of Neat Alkanes: the Viscosity Dependence of Rotational Relaxation, Yuhong Zhang, Richard M. Venable and Richard W. Pastor, *J. Phys. Chem.* 100, 2652-2660 (1996).

40. Time Scales of Lipid Dynamics and Molecular Dynamics, Richard W. Pastor and Scott E. Feller, in *Membrane Structure and Dynamics* (ed. K.M. Merz and B. Roux, Birkhauser, Boston, 1996), pp. 3-29.

41. On Simulating Lipid Bilayers with an Applied Surface Tension: Periodic Boundary Conditions and Undulations, Scott E. Feller and Richard W. Pastor, *Biophysical Journal* 71, 1350-1355 (1996).

42. Diffusion Limited First Contact of the Ends of a Polymer: Comparison of Theory and Simulation, Richard W. Pastor, Robert Zwanzig and Attila Szabo, *J. Chem. Phys.* 105, 3878-3882 (1996).

43. The Effect of Electrostatic Force Truncation on Interfacial and Transport Properties of Water, Scott E. Feller, Richard W. Pastor, Atipat Rojnuckarin, Steven Bogusz, and Bernard R. Brooks, *J. Phys. Chem.* 100, 17011-17020 (1996).

44. The Length Scales of Lipid Dynamics and Molecular Dynamics, Scott E. Feller and Richard W. Pastor, in *Proceedings of the 1997 Pacific Symposium in Biocomputing*, (ed. R.B. Altman, A.K. Dunker, L.Hunter, T.E. Klein, World Scientific, Singapore, 1997), pp. 142-150.

45. Molecular Dynamics Simulation of Unsaturated Lipid Bilayers at Low Hydration: Parametrization and Comparison with Diffraction Studies, Scott E. Feller, Daxu Yin, Richard W. Pastor and Alexander D. MacKerell, Jr. *Biophysical Journal*, 73, 2269-2279 (1997).

46. Computer simulation of a DPPC phospholipid bilayer: Structural Changes as a Function of Molecular Surface area, Scott E. Feller, Richard M. Venable and Richard W. Pastor, *Langmuir* 13, 6555-6561 (1997).

47. Time Correlation Functions, Richard W. Pastor, in *Encyclopedia for Computational Chemistry* (ed. P.R. Schleyer, John Wiley & Sons, UK, 1998).

48. Solution Structure of the Linked Cell Attachment Modules of Mouse Fibronectin Containing the RGD and Synergy Regions: Comparison with the Human Fibronectin Crystal Structure, Valerie Copie, York Tomita, Steven K. Akiyama, Shin-ichi Aota, Kenneth M. Yamada, Richard M. Venable, Richard W. Pastor, Susan Krueger and Dennis A. Torchia *J. Mol. Biol.* 277, 663-682 (1998).

Richard W. Pastor, Ph.D.

Publications (cont.)

49. Constant Surface Tension Simulations of Lipid Bilayers: the Sensitivity of Surface Areas and Compressibilities, Scott. E. Feller and Richard W. Pastor, *J. Chem. Phys.* 111, 1281-1287 (1999).

50. Distinguishing Anisotropy and Flexibility of the Pentasaccharide LNF-1 in Solution by Carbon-13 NMR Relaxation and Hydrodynamic Modeling, Torgny Rundlöf, Richard M. Venable, Richard W. Pastor, Jozef Kowalewski and Göran Widmalm, *J. Am. Chem. Soc.* 121, 11847-11854 (1999).

51. Statistical Considerations in the Establishment of Release Criteria for Allergen Vaccines, in *Proceedings of the 1999 Paul Ehrlich Symposium*, Jay E. Slater, Albert A. Gam, Maneesha D. Solanki, Suzann H. Burk, Faith M. May and Richard W. Pastor (ed. R. Kurth and D. Haustein, GIT VERLAG. Darmstadt, 2000), pp. 47-56.

52. The Determination of Equivalent Doses of Standardized Allergen Vaccines, Jay E. Slater and Richard W. Pastor, *J. Allergy and Clinical Immunology* 105, 468-474 (2000)

53. The Stability of House Dust Mite Allergens in Glycerinated Extracts. Lyudmila N. Soldatova, Elizabeth J. Paupore, Suzann H. Burk, Richard W. Pastor and Jay E. Slater, *J. Allergy and Clinical Immunology* 105, 482-488 (2000).

54. Molecular Dynamics Simulations of Gel ($L_{\beta'}$) Phase Lipid Bilayers in Constant Pressure and Constant Surface Tension Ensembles, Richard M. Venable, Bernard R. Brooks and Richard W. Pastor, *J. Chem. Phys.* 112, 4822-4832 (2000).

55. Molecular Dynamics Simulations of Octyl Glucoside Micelles: Structural Properties, Stephen Bogusz, Richard M. Venable and Richard W. Pastor, *J. Phys. Chem. B* 104, 5462-5470 (2000).

56. ICAM-1 Enhances MHC-peptide Activation of CD8+ T-cells without an Organized Immunological Synapse, Julia S. Goldstein, Trina Chen, Elena Gubina, Richard W. Pastor and Steven Kozolowski, *European J. Immunology*, 30, 3266-3279 (2000).

57. Molecular Dynamics Simulations of Octyl Glucoside Micelles: Dynamic Properties, Stephen Bogusz, Richard M. Venable and Richard W. Pastor, *J. Phys. Chem. B* 105, 8312-8321 (2001).

58. Molecular Dynamics Simulations of Water Wires and Water/Octane Model Systems, Richard M. Venable and Richard W. Pastor. *J. Chem. Phys.* 116, 2663-2664 (2002).

59. Simulations of Membranes and Other Interfacial Systems Using $P2_1$ and Pc Periodic Boundary Conditions, Elizabeth A. Dolan Richard M. Venable, Richard W. Pastor and Bernard R. Brooks, *Biophysical Journal* 85, 2317-2325 (2002).

60. Lipid Bilayers, NMR Relaxation, and Computer Simulations, Richard W. Pastor, Richard M. Venable, Scott E. Feller. *Accounts of Chemical Research* 35, 438-446 (2002).

61. Micelle-Bound Conformation of a Hairpin-Forming Peptide: A Combined NMR and Molecular Dynamics Study. Ann M. Dixon, Richard M. Venable, Richard W. Pastor and T.E. Bull, *Biopolymers* 65, 284-298 (2002).

Richard W. Pastor, Ph.D.

Publications (cont.)

62. Application of NMR, Molecular Simulation and Hydrodynamics to Conformational Analysis of Trisaccharides, Ann M. Dixon, Richard M. Venable, Göran Widmalm, T.E. Bull and Richard W. Pastor, *Biopolymers, in press.*

63. Sample Size Considerations for Establishing Clinical Bioequivalence of Allergen Formulations. in *Proceedings of the 2002 Paul Ehrlich Symposium.* Ronald L. Rabin, Jay E. Slater, Peter Lachenbruch, Richard W. Pastor, *in press.*

FDA Guidance Documents:

Testing Limits in Stability Protocols for Standardized Grass Pollen Extracts

Potency Limits for Standardized Dust Mite and Grass Allergen Vaccines: A Revised Protocol